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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/528,073	VALKNA ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-23 and 27-33* is/are pending in the application.

4a) Of the above claim(s) *27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-23 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 19-23 and 27-33 are all the pending claims for this application.

2. Claim 26 was cancelled and Claims 19-21, 23, and 31-33 were amended in the Response of 7/10/09.

3. Claims 27-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b).

4. Claims 19-23 and 31-33 are all the pending claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for objection and rejection. This action is final.

Withdrawal of Objections

Specification

6. The objection to the legend to Figure 2 as having the same description for panels 2A and 2C and the same description for panels 2B and 2D is withdrawn.

Applicants have amended the figure legend in the Response of 7/10/09 to describe the data depicted in each of the panels.

Withdrawal of Rejections

Claim Rejections - 35 USC § 101

7. The rejection of Claim 23 under 35 U.S.C. 101 because of the claimed recitation for a "medical use" is withdrawn.

Applicants have amended the claim to indicate that cellular uptake of the fusion protein occurs in a cell in vitro.

Claim Rejections - 35 USC § 112, first paragraph

Enablement

8. The rejection of Claims 23 and 26 under 35 U.S.C. 112, first paragraph because the specification does not reasonably provide enablement for a therapeutic use of the fusion protein in any subject in vivo for any disease including cancer much less where the subject is a human is withdrawn.

Applicants have cancelled Claim 26 and amended Claim 23 in the Response of 7/10/09 to recite that the transfected host cell is in vitro. Applicants comments on pp. 6-7 of the Response of 7/10/09 and the Stocks reference are acknowledged.

Claim Rejections - 35 USC § 102

9. The rejection of Claims 19, 22, 23 and 26 under 35 U.S.C. 102(b) as being anticipated by Zhao et al. (J. Method. Immunol. 254:137-145 (2001); cited in the PTO 892 form of 2/12/08) as evidenced by Pavlinkova et al. (J. Immunol. Methods 201:77-88 (1997)) is withdrawn for Claims 19, 22 and 23 and moot for cancelled Claim 26.

Applicants have amended the claims to indicate the structure of the recombinant protein and its being expressed from an expression vector in a transfected host cell, and neither of which Zhao nor Pavlinkova disclose.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. The rejection of Claims 19, 22, 23 and 33 under 35 U.S.C. 102(b) as being anticipated by Rothbard (WO 98/52614; cited in the PTO 892 form of 2/12/08) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

"Rothbard teaches poly -Arg peptides of from 4-9 residues (p. 7) or from 6 to 25 subunits (p. 10) for use as cell membrane transport peptides of selected agents across any number of biological membranes (p. 6, lines 1-7). Rothbard explicitly teaches delivering antibodies or antibody fragments such as scfv to the cytosol by attaching the transport polymers to the scfv, and that "the principle obstacle to wide application of this technology has been efficiency of uptake into infected cells" (p. 25, lines 10-21). Rothbard explicitly teaches fusion polypeptides comprising the polypeptide of interest and the transport peptide (p. 15, lines 15-20; p. 25, lines 29-31). Rothbard teaches that targets can be visualized with the fusion proteins (Example 4) and using the fusion proteins in pharmaceutical compositions (p. 7, lines 9-12)."

The rejection was maintained in the Office Action of 2/12/09 as follows:

"Applicants' allegations on p. 14 of the response of 11/21/08 have been considered and are not found persuasive. Applicants allege "Rothbard et al. reference, Example no 4 teach Arg peptides that are conjugated with a fluorescent marker. However, the present claims encompass a recombinant fusion protein comprising at least (a) a scFv-part of an antibody, and (b) a cell penetrating transport peptide. Claim 21 is further distinguished in that this claim recites that the cell penetrating transport peptide is comprised of at least a part of Transportan, Transportan 10 or Arg 9. Rothbard et al. do not teach said protein either in conjugation or fusion with Arg peptides."

Response to Arguments

Rothbard teaches on p. 13, lines 15-20:

"B. Fusion Polypeptides

Transport peptide polymers of the invention can be attached to biologically active polypeptide agents by recombinant means by constructing vectors for fusion proteins comprising the polypeptide of interest and the transport peptide, according to methods well known in the art. Generally, the transport peptide component will be attached at the C-terminus or N-terminus of the polypeptide of interest, optionally via a short peptide linker",

which when taken in view of Rothbards further disclosure for scFv and cell membrane transport peptides, is considered to read on and therefore anticipate at least generic claim 19.

As regards Claim 21 for reciting "at least a part of", the examiner submits Rothbard teaches subunit ranges for polyarginine peptides, which is considered to represent "at least a part of Arg 9."

Applicants allegations on pp. 8-9 of the Response of 7/10/09 have been considered but are not found persuasive.

A) Applicants allege Rothbard does not teach recombinant fusion proteins and therefore the claims are not anticipated by Rothbard. Moreover, Applicant has replaced the verb 'comprising' with the verb 'consisting of', whereby a fluorescence marker cannot be a part of the protein here.

Response to Arguments

Applicants attention is redirected to the excerpted passage from the previous Office Action, namely, lines 15-20 on p. 13 of Rothbard who specifically teaches a polypeptide of interest linked to a transport peptide by a short linker and where the molecule is produced by recombinant means using expression vectors. A polypeptide of interest is a scfv where Rothbard discloses at lines 10-21 on p. 23:

> "In another embodiment, the invention is useful for delivering immunospecific antibodies or antibody fragments to the cytosol to interfere with deleterious biological processes such as microbial infection. Recent experiments have shown that intracellular antibodies can be effective antiviral agents in plant and mammalian cells (e.g., Tavladoraki et al., 1993; and Shaheen et al., 1996). These methods have typically used single-chain variable region fragments (scFv), in which the antibody heavy and light chains are synthesized as a single polypeptide. The variable heavy and light chains are usually separated by a flexible linker peptide (e.g., of 15 amino acids) to yield a 28 kDa molecule that retains the high affinity ligand binding site. The principal obstacle to wide application of this technology has been efficiency of uptake into infected cells. But by attaching transport polymers to scFv fragments, the degree of cellular uptake can be increased, allowing the immunospecific fragments to bind and disable important microbial components, such as HIV Rev, HIV reverse transcriptase, and integrase proteins."

B) Applicants allege "As regards to claim 20, Rothbard does not teach GLI1 or GLI3 and Claim 21 has been amended to depend from Claim 20.

Response to Arguments

Claim 20 was not included in the original rejection and in view of Claim 21 being amended to depend from Claim 20 the examiner has withdrawn the rejection with respect to Claim 21.

The rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. The rejection of Claims 19, 20, 22, and 23 under 35 U.S.C. 103(a) as being unpatentable over Zhao et al. (J. Method. Immunol. 254:137-145 (2001); cited in the PTO 892 form of 2/12/08) as evidenced by Pavlinkova et al. (J. Immunol. Methods

201:77-88 (1997)) in view of Toftgard (WO 01/12655; cited in the PTO 892 form of 2/12/08) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

"The claimed fusion proteins were prime facie obvious at the time of the invention over Zhao as evidenced by Pavlinkova in view of Toftgard.

Zhao discloses cross-linking an MTS peptide (membrane translocating sequence) derived from the signal region of Kaposi fibroblast growth factor to the 5D10 monoclonal antibody in order to render the antibody cell- permeable for live cells in vitro (e.g., Figure 4), where the complex is diluted in PBS and administered to cells in vitro. This is interpreted as reading on a pharmaceutical composition. The complex allows visualization of intracellular antigens for diagnostic purposes. Zhao teaches that the approach of linking an MST can be performed on any antibody (p. 144, Col. 2, last line). Zhao teaches thru incorporation by reference to Pavlinkova that small peptides can be introduced into scfv antibodies, providing as indirect support, the modification of scfvs to include cell membrane transport peptides. Zhao appreciates introducing cell membrane penetrating peptides into unlimited antibodies including scfvs as further evidenced by Pavlinkova, but does not teach scfvs for the family of GLI proteins for GLI-1 or GLI-3, whereas does Toftgard.

Toftgard discloses the GLI-1 protein (see entire document) and the GLI-3 protein (pp. 3, 24 and 36) and making antibodies against these intracellular antigens (p. 12, lines 1-14). Included amongst the antibodies are single chain antibodies and pharmaceutical compositions comprising the antibodies and carriers (p. 3, line 25; p. 12, lines 16-20; p. 13, lines 10-15). Toftgard teaches the technology for making protein fusion constructs in general (p. 28, lines 15-16).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide based on the combined disclosures of Zhao as evidenced by Pavlinkova in view of Toftgard. All of the references appreciate and expressly teach the utility of scfv antibodies. Thus in order to visualize an intracellular antigen such as GLI-1 and GLI-3 as taught by Toftgard or the intracellular antigen of Zhao, the ordinary artisan would have been motivated to have modified an antibody into a scfv not only to decrease the size, but to include a cell membrane permeating peptide such as taught by Zhao in order to facilitate or increase cellular uptake of the antibody into a cell in vitro. In order to detect or visualize an intracellular antigen that was otherwise not accessible to the antibody without permeabilizing the cell itself, one would have been motivated to have engineered a fusion protein where Toftgard and Pavlinkova provided the methods for making fusion constructs and more especially Pavlinkova's teaching of scfvs, to include a cell penetrating peptide based on Zhao. The ordinary artisan would have been motivated at the time of the invention to engineer the cell penetrating peptide to the scfv so that whole cells could be examined in vitro without affecting cell structure or viability (see Zhao at p. 138, Col. 1, ¶1). The ordinary artisan would have been motivated in producing the fusion protein for a diagnostic visualization of intracellular antigen expression in screening cells in vitro and where the fusion protein was formulated into a pharmaceutical composition compatible for administration to living cell in vitro. The ordinary artisan would have been reasonably assured of success in having produced or used the fusion protein for limited applications in vitro because the methods and materials for scfvs and cell penetrating peptides were already available based on the combined disclosures of the cited references, the construction of fusion proteins was already well known based on the combined disclosures of Toftgard and Pavlinkova, and producing a scfv by introduction of a peptide in order to facilitate cellular uptake of the antibody had already been accomplished by Zhao as evidenced by Pavlinkova. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Zhao as evidenced by Pavlinkova and Toftgard.

The rejection was maintained in the Office Action of 2/12/09 as follows:

"Applicants' allegations on pp. 16 and 17 of the Response of 11/21/08 and the extrinsic experimental evidence provided in Exhibit A have been considered but are not found persuasive. Applicants allege 'there are no teachings of the scFv-part of an antibody. Neither Zhao et al., nor Toftgard provide any information on how a scFv peptide behaves when linked to a penetrating transport peptide within a cell"; and fusion proteins are unpredictable in activity and this depends on where the cell penetrating transport peptide is fused with respect to the GLI protein based on the extrinsic experimental data.

Response to Arguments

Contrary to Applicants initial assertion, both Zhao as evidenced by Pavlinkova and Toftgard explicitly teach recombinant fusion proteins comprising a recombinant scFv antibody where Toftgard further teaches linking these antibody fragments by recombinant technology to other protein molecules. Zhao teaches cellular uptake for a Mab conjugated with a cell penetrating peptide, and as evidenced by Pavlinkova, insertion of small molecules into a scFv antibody can be accomplished by cross-linking chemistry (see p. 145, Col. 1 of Zhao referencing Pavlinkova). The

skilled artisan would recognize that a scFv is itself a recombinant protein generated by recombinant technology from a parent antibody (see p. 3, lines 2-10 and pp. 8-9 of the specification). Thus the instant claimed "recombinant fusion protein" comprises a recombinant "scFv-part of an antibody." The claims do not distinguish which portion of the fusion protein is recombinant. The claims do not distinguish the recombinant scfv portion of the protein being conjugated or recombinant fused to a cell penetrating transport peptide.

The ordinary artisan reviewing the extrinsic data in Exhibit A comparing the scFv anti-GLi3 antibody (5E1) having a C-terminal fusion to transportan (5E1-Tr), the 5E1 antibody alone and the 5E1 antibody chemically linked to Trp 10 (5E1 + TP10) could reasonably conclude that:

a) full length transportan fused to the C-terminus of the 5E1 scFv does not mediate cell uptake into Cos-7 cells;

b) transportan 10 chemically linked to 5E1 scfv mediates cell uptake into Cos-7 cells;

c) it is not clear if transportan 10 fused to the C-terminus of 5E1scfv would mediate uptake into Cos-7 cells;

d) it is not clear if transportan fused to the N-terminus of 5E1 scfv would mediate uptake into Cos-7 cells; and

e) it is not clear where transportan 10 binds to the 5E1 scfv under chemical linkage.

Rather than considering the generation of fusion proteins unpredictable as alleged by Applicants, the ordinary artisan could only conclude these data are inconclusive because of the lack of unmatched controls and the number of questions that are raised rather than answered.

Additionally, the submission of these new data as an exhibit with the actual Response absent any attestation to the facts by the actual inventors is not compliant under 37 CFR 1.132. 37 CFR 1.132 states in part: "when any claim for an application is rejected to..., any evidence submitted to traverse the rejection...on a basis not otherwise provided for must be by way of an oath or declaration under this section." The purpose of an a 1.132 declaration is to provide a means for submitting evidence to overcome a rejection, and the kind of evidence in the instant case does not fall under an exception.

Applicants allegations on pp. 9-10 of the Response of 7/10/09 and the 1.132 Declaration of Dr. Kogerman have been carefully considered and are not found persuasive.

A) Applicants allege even if one skilled in the art would recognize that a scFv is itself a recombinant protein generated by recombinant technology from a parent antibody, she/he would not enter the instant invention as claimed in the amended claims by combining Toftgard teaching with the teaching with Zhao. Only by unpermitted hindsight can one conclude that one skilled in the art would have been motivated to have modified an antibody into a scfv and to express a peptide including the scfv, a linker and a cell membrane permeating peptide from a vector cloned into a host cell as is claimed in the amended claims. Accordingly, applicant respectfully request

Response to Arguments

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As found by the Examiner, the combined references teach all of the instant claimed elements, and expressing the fusion protein as a contiguous protein from an expression vector would have provided more than sufficient motivation to modify a fusion protein otherwise produced by step-wise chemical synthesis for each of the elements especially where the references teach all of the elements and the technology for producing a recombinant protein.

Additionally it is not a requirement that the Examiner establish that a given cited art reference contains all the elements of the rejected claim, as the analysis under 35 U.S.C. § 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR, 550 U.S. at 418.

B) Applicants and the Declaration evidence allege that that without experimental data one cannot predict the internalization of the fusion molecule into the cell when

comparing two different cell types (COS-7 vs HEK-293 cells) using the same fusion construct (e.g., Figures 4A, 4B and 4C in the Declaration).

Response to Arguments

Once again, and at least for Figures 4A and 4B the examiner is left with having to discern experimental data where the test and control photos each appear as having no stained cells whatsoever. Neither Figure 4A nor 4B shows a positive or negative control that is visible in the copies provided. Secondly, while the explanation on p. 4 of the Declaration indicates that Figure 4C shows four different stained groups, no photo labeled "Figure 4C" is enclosed with the Declaration, but if the histogram on p. 6 is representative of Figure 4C, then only three groups appears in the figure. Additionally, it is impossible to tell which of the sample groups are shown in this figure because no groups are labeled. The Declaration appears to have been assembled rather hastily and does not assist in advancing the prosecution.

C) Applicants and the Declarant then allege that the length of the linker for the fusion protein is critical to obtaining a functional fusion molecule.

Response to Arguments

The claims are not limited to the length or kind of linker. If linker length is critical to function or performance in order for the claims to be enabled for using the fusion protein, then Applicants are encouraged to introduce limitations for the criticality of the size of the linker. Finally, the Declarant does not so much as describe the linker or the length of the linker. There is some vague reference on p. 4 of the Declaration for linkers

"a tandem repeats (2xlinker adn 3x linker sequence)." How do these experimental linkers compare to the linker of the cited references?

The rejection is maintained.

12. The rejection of Claims 19-23, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Zhao et al. (J. Method. Immunol. 254:137-145 (2001); cited in the PTO 892 form of 2/12/08) as evidenced by Pavlinkova et al. (J. Immunol. Methods 201:77-88 (1997)) in view of in view of Toftgard (WO 01/12655; cited in the PTO 892 form of 2/12/08) as applied to claims 19, 20, and 23 above, and further in view of Rothbard (WO/ 98/52614; cited in the PTO 892 form of 2/12/08) and Lindgren et al. (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

"The claimed fusion proteins were prime facie obvious at the time of the invention over Zhao as evidenced by Pavlinkova in view of Toftgard and further in view of Rothbard and Lindgren.

The interpretation of Zhao as evidenced by Pavlinkova in view of Toftgard is discussed above under section 14. Zhao appreciates intracellular targeting of antibody scfv's using membrane penetrating peptides conjugated to scfv, and Toftgard and Pavlinkova appreciate scfvs and making fusion protein constructs, but do no expressly teach the peptides for transportan, transportan 10 or Arg9, whereas do Rothbard and Lindgren.

Rothbard teaches poly -Arg peptides of from 4-9 residues (p. 7) or from 6 to 25 subunits (p. 10) for use as cell membrane transport peptides of selected agents across any number of biological membranes (p. 6, lines 1-7). Rothbard explicitly teaches delivering antibodies or antibody fragments such as scfv to the cytosol by attaching the transport polymers to the scfv, and that "the principle obstacle to wide application of this technology has been efficiency of uptake into infected cells" (p. 25, lines 10-21).

Lindgren teaches cell penetrating peptides for transportan (Table 1, Table 2, p. 99, Col. 1), and the use of this and other peptides for cellular delivery of drugs or research tools (p. 102, Col. 2).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide based on the combined disclosures of Zhao as evidenced by Pavlinkova in view of Toftgard and further in view of Rothbard and Lindgren. Zhao as evidenced by Pavlinkova in view of Toftgard provide the motivation to produce fusion proteins comprising a sfv and a cell membrane penetrating peptide to facilitate transport of the scfv into a viable cell in vitro for whole cell visualization of the targeted antigen. One skilled in the art would have found more than sufficient motivation to substitute different cell membrane penetrating peptides in the fusion protein comprising the scfv based on Zhao and Rothbard because each explicitly teach the advantages of small antibody forms like scfv and transport peptides which could be used to facilitate cell entry of the scfv. Rothbard and Lindgren teach different structural

classes of transport peptides encompassing transportan and Arg 9 and provide the explicit motivation to use the peptides to convey molecules across cell membranes that would otherwise be impermeable. The ordinary artisan would have been reasonably assured of success in having produced the fusion proteins and used them to visualize a target antigen in vitro in whole, living cells because as between all of the references all of the methods and reagents were already available and had been shown to work in related molecules for similar purposes. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Zhao as evidenced by Pavlinkova and Toftgard in view of Rothbard and Lindgren.

The rejection was maintained in the Office Action of 2/12/09 as follows:

"Applicants allegations on p. 16 and 17 of the Response of 11/21/08 and the extrinsic experimental evidence provided in Exhibit A have been considered but are not found persuasive. Applicants allege 'there are no teachings of the scFv-part of an antibody. Neither Zhao et al., nor Toftgard provide any information on how a scFv peptide behaves when linked to a penetrating transport peptide within a cell"; "Lindgren et al. teach intracellular delivery of cell penetrating peptides, in particular, the properties of Transportan as a transporter peptide, however, none of the references teach the claimed fusion protein (as now claimed) or the substitutions of known sequences for another to obtain predictable results yielding the claimed fusion proteins"; and fusion proteins are unpredictable in activity and this depends on where the cell penetrating transport peptide is fused with respect to the GLI protein based on the extrinsic experimental data.

Response to Arguments

See the examiners comments under section 13 above as they apply here regarding the primary references, the inconclusiveness of the extrinsic evidence and Applicants' non-compliance under 37 CFR 1.132 for submission of these data.

Applicants allegations on pp. 9-10 of the Response of 7/10/09 have been considered and are not found persuasive. Applicants allege as is discussed above, Zhao et al. teaches conjugate proteins, Toftgard teaches peptides consisting of fragments of GLI-1 and SUFUH and monoclonal antibodies and antibody fragments specifically binding to these proteins. Rothbard teaches Arg9 as a transport peptide and Lindgren teaches transportan as transporter peptide. The amended claims are toward a recombinant fusion protein that consists of scFv portion, a linker and a transport peptide expressed from a vector cloned into a host cell.

Response to Arguments

The examiner's comments set forth under section 11 above are incorporated by reference. In addition, as found by the Examiner, the combined references teach all of the instant claimed elements, and expressing the fusion protein as a contiguous protein

from an expression vector would have provided more than sufficient motivation to modify a fusion protein otherwise produced by step-wise chemical synthesis for each of the elements. The rejection is maintained.

13. The rejection of Claims 19, 22, 23, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Rothbard (WO 98/52614; cited in the PTO 892 form of 2/12/08) in view of Lindgren et al. (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

"The claimed fusion proteins were prime facie obvious at the time of the invention over Rothbard in view Lindgren.

Rothbard teaches poly -Arg peptides of from 4-9 residues (p. 7) or from 6 to 25 subunits (p. 10) for use as cell membrane transport peptides of selected agents across any number of biological membranes (p. 6, lines 1-7). Rothbard explicitly teaches delivering antibodies or antibody fragments such as scfv to the cytosol by attaching the transport polymers to the scfv, and that "the principle obstacle to wide application of this technology has been efficiency of uptake into infected cells" (p. 25, lines 10-21). Rothbard explicitly teaches fusion polypeptides comprising the polypeptide of interest and the transport peptide (p. 15, lines 15-20; p. 25, lines 29-31). Rothbard teaches that targets can be visualized with the fusion proteins (Example 4) and using the fusion proteins in pharmaceutical compositions (p. 7, lines 9-12). Rothbard explicitly teaches transport peptides fused to scfv but does not disclose transportan as a species whereas does Lindgren.

Lindgren teaches cell penetrating peptides for transportan (Table 1, Table 2, p. 99, Col. 1), and the use of this and other peptides for cellular delivery of drugs or research tools (p. 102, Col. 2).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide at the time of the invention based on the combined disclosures of Rothbard in view Lindgren. One skilled in the art would have been motivated to produce fusion proteins comprising a sfv and a cell membrane penetrating peptide to facilitate transport of the scfv into a viable cell in vitro for whole cell visualization of the targeted antigen based on the disclosure or Rothbard alone. One skilled in the art would have found more than sufficient motivation to substitute different cell membrane penetrating peptides in the fusion protein comprising the scfv based on Rothbard because Rothbard explicitly teaches the advantages of small antibody forms like scfv and transport peptides such as Arg 9 peptides which could be used to facilitate cell entry of the scfv, and Lindgren teaches different structural classes of transport peptides encompassing transportan to deliver agents into cells that would otherwise be impermeable. The ordinary artisan would have been reasonably assured of success in having produced the fusion proteins and used them to visualize a target antigen in vitro in whole, living cells because as between all of the references, all of the methods and reagents were already available and had been shown to work in related molecules for similar purposes. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Rothbard and Lindgren.

The rejection was maintained in the Office Action of 2/12/09 as follows:

"Applicants allegations on p. 16 and 17 of the Response of 11/21/08 and the extrinsic experimental evidence provided in Exhibit A have been considered but are not found persuasive.

Response to Arguments

Rothbard teaches on p. 13, lines 15-20:

"B. Fusion Polypeptides

Transport peptide polymers of the invention can be attached to biologically active polypeptide agents by recombinant means by constructing vectors for fusion proteins comprising the polypeptide of interest and the transport peptide, according to methods well known in the art. Generally, the transport peptide component will be attached at the C-terminus or N-terminus of the polypeptide of interest, optionally via a short peptide linker", which when taken in view of Rothbards further disclosure for scFv and cell membrane transport peptides, is considered to read on and therefore anticipate or ender obvious at least generic claim 19.

The skilled artisan would recognize that a scFv is itself a recombinant protein generated by recombinant technology from a parent antibody (see p. 3, lines 2-10 and pp. 8-9 of the specification). Thus the instant claimed "recombinant fusion protein" comprises a recombinant "scFv-part of an antibody." The claims do not distinguish which portion of the fusion protein is recombinant. The claims do not distinguish the recombinant scfv portion of the protein being conjugated or recombinant fused to a cell penetrating transport peptide.

The ordinary artisan reviewing the extrinsic data in Exhibit A comparing the scFv anti-GLi3 antibody (5E1) having a C-terminal fusion to transportan (5E1-Tr), the 5E1 antibody alone and the 5E1 antibody chemically linked to Trp 10 (5E1 + TP10) could reasonably conclude that:

a) full length transportan fused to the C-terminus of the 5E1 scFv does not mediate cell uptake into Cos-7 cells;

b) transportan 10 chemically linked to 5E1 scfv mediates cell uptake into Cos-7 cells;

c) it is not clear if transportan 10 fused to the C-terminus of 5E1scfv would mediate uptake into Cos-7 cells;

d) it is not clear if transportan fused to the N-terminus of 5E1 scfv would mediate uptake into Cos-7 cells; and

e) it is not clear where transportan 10 binds to the 5E1 scfv under chemical linkage.

Rather than considering the generation of fusion proteins unpredictable as alleged by Applicants, the ordinary artisan could reasonably find these data are inconclusive because of the lack of unmatched controls and the number of questions that are raised rather than answered.

Additionally, the submission of these new data as an exhibit with the actual Response absent any attestation to the facts by the actual inventors is not compliant under 37 CFR 1.132. 37 CFR 1.132 states in part: "when any claim for an application is rejected to..., any evidence submitted to traverse the rejection...on a basis not otherwise provided for must be by way of an oath or declaration under this section." The purpose of an a 1.132 declaration is to provide a means for submitting evidence to overcome a rejection, and the kind of evidence in the instant case does not fall under an exception to this rule.

This rejection is maintained.

Applicants allegations on pp. 10-11 of the Response of 7/10/09 have been considered and are not found persuasive. Applicants allege Rothbard teaches that transport peptide polymers of his invention can be attached to biologically active polypeptide agents by recombinant means by constructing vectors for fusion proteins comprising the polypeptide or interest and the transport peptide, and that the transport peptide polymers Rothbard teaches are poly-Arg peptides and the biologically active polypeptide agent encompasses almost any biologically active agents as is disclosed on page 4 lines 11-23 of Rothbard.

Response to Arguments

Applicants attention is redirected to the excerpted passage from the previous Office Action, namely, lines 15-20 on p. 13 of Rothbard who specifically teaches a polypeptide of interest linked to a transport peptide by a short linker and where the molecule is produced by recombinant means using expression vectors. A polypeptide of interest is a scfv where Rothbard discloses at lines 10-21 on p. 23:

> "In another embodiment, the invention is useful for delivering immunospecific antibodies or antibody fragments to the cytosol to interfere with deleterious biological processes such as microbial infection. Recent experiments have shown that intracellular antibodies can be effective antiviral agents in plant and mammalian cells (e.g., Tavladoraki et al., 1993; and Shaheen et al., 1996). These methods have typically used single-chain variable region fragments (scFv), in which the antibody heavy and light chains are synthesized as a single polypeptide. The variable heavy and light chains are usually separated by a flexible linker peptide (e.g., of 15 amino acids) to yield a 28 kDa molecule that retains the high affinity ligand binding site. The principal obstacle to wide application of this technology has been efficiency of uptake into infected cells. But by attaching transport polymers to scFv fragments, the degree of cellular uptake can be increased, allowing the immunospecific fragments to bind and disable important microbial components, such as HIV Rev, HIV reverse transcriptase, and integrase proteins."

The rejection is maintained.

14. The rejection of Claims 19-23, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Rothbard (WO 98/52614; cited in the PTO 892 form of 2/12/08) in view of Lindgren et al. (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08) as applied to claims 19, 21, and 23 above, and further in view of Toftgard (WO 01/12655; cited in the PTO 892 form of 2/12/08) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

"The claimed fusion proteins were prime facie obvious at the time of the invention over Rothbard in view Lindgren and Toftgard.

The interpretation of Rothbard in view Lindgren is discussed above under section 17. Rothbard appreciates scfv directed against many different target antigens and using the scfvs in the form of a fusion protein with a transport peptide to mediate or facilitate uptake but does not disclose the scfv recognizing GLI proteins such as GLI-1 and GLI-3, whereas does Toftgard.

Toftgard discloses the GLI-1 protein (see entire document) and the GLI-3 protein (pp. 3, 24 and 36) and making antibodies against these intracellular antigens (p. 12, lines 1-14). Included amongst the antibodies are single chain antibodies, and pharmaceutical compositions comprising the antibodies and carriers (p. 3, line 25; p. 12, lines 16-20; p. 13, lines 10-15). Toftgard teaches the technology for making protein fusion constructs in general (p. 28, lines 15-16).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide at the time of the invention based on the combined disclosures of Rothbard and Lindgren in view of Toftgard. Rothbard and Toftgard appreciate and expressly teach the utility of scfv antibodies. Thus in order to visualize an intracellular antigen such as GLI-1 and GLI-3 as taught by Toftgard or an intracellular antigen of Rothbard, the ordinary artisan would have been motivated to have modified an antibody into a scfv not only to decrease the size, but to include a cell membrane permeating peptide such as taught by Rothbard and Lindgren in order to facilitate or increase cellular uptake of the antibody into a cell in vitro. In order to detect or visualize an intracellular antigen that was otherwise not accessible to the antibody without permeabilizing the cell itself, one would have been motivated to have engineered a fusion protein where Rothbard abd Toftgard provided the methods for making fusion constructs and more especially Rothbard's 's teaching of scfvs, to include a cell penetrating peptide including Arg 9 and the peptides of Lindgren. The ordinary artisan would have been motivated at the time of the invention to engineer the cell penetrating peptide to the scfv so that whole cells could be examined in vitro without affecting cell structure or viability. The ordinary artisan would have been motivated in producing the fusion protein for a diagnostic visualization of intracellular antigen expression in screening cells in vitro and where the fusion protein was formulated into a pharmaceutical composition compatible for administration to living cell in vitro. The ordinary artisan would have been reasonably assured of success in having produced or used the fusion protein for limited applications in vitro because the methods and materials for scfvs and cell penetrating peptides were already available based on the combined disclosures of the cited references, the construction of fusion proteins was already well known based on the combined disclosures of Rothbard and Toftgard, and producing a scfv by introduction of a peptide in order to facilitate cellular uptake of the antibody had already been accomplished by Rothbard. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Rothbard, Lindgren and Toftgard.

The rejection was maintained in the Office Action of 2/12/09 as follows:

"Applicants allegations on p. 16 and 17 of the Response of 11/21/08 and the extrinsic experimental evidence provided in Exhibit A have been considered but are not found persuasive.

Response to Arguments

See the examiners comments under section 15 above as they apply here regarding the primary references, the inconclusiveness of the extrinsic evidence and Applicants' non-compliance under 37 CFR 1.132 for submission of these data.

This rejection is maintained.

Applicants allegations on pp. 10-11 of the Response of 7/10/09 have been considered and are not found persuasive. Applicants allege Rothbard teaches that

transport peptide polymers of his invention can be attached to biologically active polypeptide agents by recombinant means by constructing vectors for fusion proteins comprising the polypeptide or interest and the transport peptide, and the transport peptide polymers Rothbard teaches in the publication are poly-Arg peptides and the biologically active polypeptide agent encompasses almost any biologically active agents as is disclosed on page 4 lines 11-23 of Rothbard.

Response to Arguments

Applicants attention is redirected to the excerpted passage from the previous Office Action, namely, lines 15-20 on p. 13 of Rothbard who specifically teaches a polypeptide of interest linked to a transport peptide by a short linker and where the molecule is produced by recombinant means using expression vectors. A polypeptide of interest is a scfv where Rothbard discloses at lines 10-21 on p. 23:

> "In another embodiment, the invention is useful for delivering immunospecific antibodies or antibody fragments to the cytosol to interfere with deleterious biological processes such as microbial infection. Recent experiments have shown that intracellular antibodies can be effective antiviral agents in plant and mammalian cells (e.g., Tavladoraki et al., 1993; and Shaheen et al., 1996). These methods have typically used single-chain variable region fragments (scFv), in which the antibody heavy and light chains are synthesized as a single polypeptide. The variable heavy and light chains are usually separated by a flexible linker peptide (e.g., of 15 amino acids) to yield a 28 kDa molecule that retains the high affinity ligand binding site. The principal obstacle to wide application of this technology has been efficiency of uptake into infected cells. But by attaching transport polymers to scFv fragments, the degree of cellular uptake can be increased, allowing the immunospecific fragments to bind and disable important microbial components, such as HIV Rev, HIV reverse transcriptase, and integrase proteins."

The rejection is maintained.

15. The rejection of Claims 19-23 and 31-33 under 35 U.S.C. 103(a) as being unpatentable over Rothbard (WO 98/52614; cited in the PTO 892 form of 2/12/08) in view of Toftgard (WO 01/12655; cited in the PTO 892 form of 2/12/08) and further in view of Lindgren et al. (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08) and Soomets et al. (Biochem. Biophys. Acta 1467:165-176 (2000) cited I the IDS of 11/21/08) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 2/12/09 as follows:

"Claim 19 is interpreted as being drawn to any recombinant fusion protein comprising any scfv and any cell-penetrating transport peptide where each of these elements is "at least" what comprises a fusion protein. The structure of the protein and the elements linking the two moieties are interpreted as being unlimited given the comprising language. Claims 20 is interpreted as being drawn to

Claim 20 is interpreted as being drawn to an anti- GLI protein scfv, where the protein is GLI-1 or GLI-3, and any cell-penetrating transport peptide where each of these elements is "at least" what comprises a fusion protein.

Claim 21 is interpreted as being drawn to the fusion protein of Claim 19 where the cell transport peptide is Transportan, Transportan 10 or Arg 9.

Claim 23 is interpreted as being drawn to using the fusion protein of Claim 19 to visualize an intracellular antigen for diagnosing, for example.

Claim 26 is interpreted as a pharmaceutical composition comprising the fusion protein of Claim 19.

Claims 31-33 are drawn to the fusion protein of Claim 19 where the cell-penetrating transport peptide is Transportan (Claim 31), Transportan 10 (Claim 32) or Arg 9 (Claim 33).

The claimed recombinant fusion proteins were prime facie obvious at the time of the invention over Rothbard, Toftgard, Lindgren and Soomets.

Rothbard teaches poly -Arg peptides of from 4-9 residues (p. 7) or from 6 to 25 subunits (p. 10) for use as cell membrane transport peptides of selected agents across any number of biological membranes (p. 6, lines 1-7). Rothbard explicitly teaches delivering antibodies or antibody fragments such as scfv to the cytosol by attaching the transport polymers to the scfv, and that "the principle obstacle to wide application of this technology has been efficiency of uptake into infected cells" (p. 25, lines 10-21). Rothbard explicitly teaches fusion polypeptides comprising a polypeptide of interest and the transport peptide (p. 15, lines 15-20; p. 25, lines 29-31). Rothbard teaches that targets can be visualized with the fusion proteins (Example 4) and using the fusion proteins in pharmaceutical compositions (p. 7, lines 9-12).

Toftgard discloses the GLI-1 protein (see entire document) and the GLI-3 protein (pp. 3, 24 and 36) and making antibodies against these intracellular antigens (p. 12, lines 1-14). Included amongst the antibodies are single chain antibodies, and pharmaceutical compositions comprising the antibodies and carriers (p. 3, line 25; p. 12, lines 16-20; p. 13, lines 10-15). Toftgard teaches the technology for making protein fusion constructs in general (p. 28, lines 15-16).

Lindgren teaches cell penetrating peptides for transportan (Table 1, Table 2; p. 101, Col. 1, ¶4-5), and the use of this and other peptides for cellular delivery of drugs or research tools (p. 102, Col. 2). Lindgren teaches:
"After a I min incubation at 37°C, transportan is found m the plasma membrane and its redistribution to the nuclear envelope and other intracellular membranes follows rapidly. Cellular uptake is not blocked by unlabelled transportan or galanin, or by incubation of the cells at 4°C or in hyperosmolar sucrose solution. Uptake kinetics exhibit a rapid saturation of the cells, followed by a slow leakage of the radio-iodinated peptide into the medium2s. Furthermore, transportan is enriched in cells, and at saturation the intracellular concentration is at least twofold higher than the extracellular concentration2s. At concentrations $\leq$ 20 μM, transportan shows no apparent toxicity" (p. 101, Col. 1, ¶5).

Soomets teaches generating peptide mutants based on the wild-type transportan to generate transportan 10 as shown in Table I on p. 691. Transportan 10 internalized to a comparable degree with tranpsortan at different temperatures, The peptide was detected in the cytoplasm and nucleus of Bowes cells, accumulating mainly in the intracellular membranous structures and nuclear envelope (p. 170, Col. 1 to Col. 2; Figure 1). Soomets teaches TP and TP10 penetrate into different cells in rapid and efficient way, the penetration is energy independent and not receptor-mediated. Soomets teaches:
"...we have synthesized several shorter TP analogies that retain the efficient cell penetration property of the parent compound. One of these, TP10, does not modulate the basal GTPase activity even at bery high concentrations nor is it recognized by galanin receptors. These features make TP10 a promising candidate for a new generation of transporter peptide with significantly less potential side effects" (p. 175, Col. 2).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide at the time of the invention based on the combined disclosures of Rothbard, Toftgard, Lindgren and Soomets. Rothbard and Toftgard appreciate and expressly teach the utility of scfv antibody size in penetrating tissues. Thus in order to visualize an intracellular antigen such as GLI-1 and GLI-3 as taught by Toftgard or an intracellular antigen of Rothbard, the ordinary artisan would have been motivated to have modified an antibody into a scfv not only to decrease the size, but to include a cell membrane permeating peptide such as taught by Rothbard and Lindgren and Soomets in order to facilitate much less increase cellular uptake of the scfv antibody into a cell in vitro. In order to detect or visualize an intracellular antigen such as GLI-1 or GLI-3 as taught by Toftgard that was otherwise not accessible to an antibody without permeabilizing the cell itself, one would have been motivated to have engineered a fusion protein where Rothbard and Toftgard provided the methods for making fusion constructs for scfv and more especially Rothbard's 's teaching of scfvs, to include a cell penetrating peptide including Arg 9 and further in view of the peptides of Lindgren and Soomets. The ordinary artisan would have been motivated at the time of the invention to engineer the cell penetrating peptide to the scfv so that whole cells could be examined in vitro without affecting cell structure or viability. The ordinary artisan would have been motivated in producing the fusion protein for a diagnostic visualization of intracellular antigen expression in screening cells in vitro and where the fusion protein was formulated into a pharmaceutical composition compatible for administration to living cell in vitro to visualize GLI-1 and GLI-3. The ordinary artisan would have been reasonably assured of success in having produced or used the fusion protein for limited applications in vitro because the methods and materials for scfvs and cell penetrating peptides were already available based on the combined disclosures of the cited references, the construction of fusion proteins was already well known based on the combined disclosures of Rothbard and Toftgard, producing a scfv by introduction of a peptide in order to facilitate cellular uptake of the antibody had already been accomplished by Rothbard, and cell-membrane penetrating peptides were already known to be more effective than others based on Rothbard, Lingard and Soomets. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Rothbard, Lindgren, Toftgard and Soomets.

Applciants allegations on pp. 12-14 of the Response of 7/10/02 have been considered and are not found persuasive. Applicant is of the opinion that Examiner's conclusion of obviousness is based on improper hindsight reasoning and that the Examiner is applying an improper 'obvious to try' rational in support of an obviousness rejection.

Response to Arguments

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Additionally, it is not a requirement that the Examiner establish that the cited art contains all the elements of the rejected claim, as the analysis under 35 U.S.C. § 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR, 550 U.S. at 418.

As found by the Examiner, the combined references teach all of the instant claimed elements, and expressing the fusion protein as a contiguous protein from an expression vector would have provided more than sufficient motivation to modify a fusion protein otherwise produced by chemical synthesis for each of the elements. Applicants attention is redirected to the excerpted passage from the previous Office Action, namely, lines 15-20 on p. 13 of Rothbard who specifically teaches a polypeptide of interest linked to a transport peptide by a short linker and where the molecule is produced by recombinant means using expression vectors. A polypeptide of interest is a scfv where Rothbard discloses at lines 10-21 on p. 23:

> "In another embodiment, the invention is useful for delivering immunospecific antibodies or antibody fragments to the cytosol to interfere with deleterious biological processes such as microbial infection. Recent experiments have shown that intracellular antibodies can be effective antiviral agents in plant and mammalian cells (e.g., Tavladoraki et al., 1993; and Shaheen et al., 1996). These methods have typically used single-chain variable region fragments (scFv), in which the antibody heavy and light chains are synthesized as a single polypeptide. The variable heavy and light chains are usually separated by a flexible linker peptide (e.g., of 15 amino acids) to yield a 28 kDa molecule that retains the high affinity ligand binding site. The principal obstacle to wide application of this technology has been efficiency of uptake into infected cells. But by attaching transport polymers to scFv fragments, the degree of cellular uptake can be increased, allowing the immunospecific fragments to bind and disable important microbial components, such as HIV Rev, HIV reverse transcriptase, and integrase proteins."

Once again, and at least for Figures 4A and 4B in the Declaration, the examiner is left with having to discern experimental data where the test and control photos each appear as having no stained cells whatsoever. Neither Figure 4A nor 4B shows a positive or negative control that is visible in the copies provided. Secondly, while the explanation on p. 4 of the Declaration indicates that Figure 4C shows four different stained groups, no photo as labeled "Figure 4C" is enclosed with the Declaration and if the histogram on p. 6 is representative of Figure 4C, then only three groups appears in the figure. Additionally, it is impossible to tell which of the sample groups are shown in this figure because no groups are labeled. The Declaration appears to have been assembled rather hastily and does not assist in advancing the prosecution.

Finally, the claims are not limited to the length or kind of linker. If linker length is critical to function or performance in order for the claims to be enabled for using the

fusion protein, then Applicants are encouraged to introduce limitations for the criticality of the size of the linker.

The rejection is maintained.

New Grounds for Objection

Claim Objections

16. Claim 23 is objected to because of the following informalities: the claim recites "allowed to enter into a human cells in vitro" and in order to substantially improve claim form, it is suggested that the noted phrase be amended to recite, *e.g.,* "allowed to enter into a human cell in vitro". Appropriate correction is required.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 recites the limitation "said protein". There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

18. Claims 19-22 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for expression of a "fusion protein" comprising a cell-penetrating transport peptide (CPP)-anti-GLi-1 or anti-GLi-3 polyclonal or monoclonal antibody, or the GLI-1 scfv or the GLI-3 scFv fused to a CPP (e.g., VL-CPP -linker-VH) by a transfected host cell *in vitro*, does not reasonably provide enablement for expressing the fusion protein in any transgenic host cell in vivo in any subject much less where the subject is a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the invention/ Skill in the Art

The claims are interpreted as follows: a recombinant fusion protein consisting of (a) scFv-part of an antibody, (b) a linker; and (c) a cell penetrating transport peptide,

wherein the protein is expressed from an expression vector cloned into any host cell where the cell is in vivo in any subject.

The relative skill in the art required to practice the invention is a clinical diagnostician with a background in antibody-based methods.

Disclosure in the Specification

The specification teaches in general that cancer-specific antibodies to cancer-specific intracellular signals can be used for treatment of diseases by modulating the uptake of the antibodies into disease-affected cells in order to inactivate the intracellular targets (p. 2, lines 17). The specification teaches that "delivery of the scFv intrabodies remains a problematic issue for their potential therapeutic applications (p. 3, lines13-14). To solve this problem, the specification teaches peptide-mediated membrane penetration to deliver antibodies or scFvs to intracellular target proteins (p. 3, lines 17-20). The specification describes the fusion proteins for use in the treatment of a disease or health disorder in "humans or animals" (p. 5, lines 1-2). The specification describes cell penetrating peptides (CPPs) such as transportan for transporting antibodies into cells (p. 4, lines 3-4).

Working examples in the specification showing expression of a recombinant fusion protein from an expression within in any cell in vivo are none. The specification is insufficient and therefore non-enabling in its disclosure for expressing any fusion protein comprising any scfv fused to any CPP by any cell in vivo in any transgenic animal much less a human.

Prior art status: gene delivery and expression in vivo is unpredictable

The claims are interpreted as encompassing a gene therapy where expression of the protein occurs in vivo in host cell.

The state of the art for gene therapy as discussed by Rochlitz C. F. (Swiss Medicine Weekly, 131:4-9, 2001) is unpredictable and Rochlitz teaches:

> "that none of the more than one hundred clinical studies performed so far had formally proven efficacy of the approach [gene therapy] in any human disease. Although anecdotal reports of tumor responses are becoming more frequent in several human malignancies, the situation has not changed dramatically." (See page 8, bottom of page). Rochlitz continue "Main problems are still the lack of vectors with high transduction efficiency in vivo, the low tumor specificity of available systems, and our incomplete knowledge of molecular tumor pathology." (see pages 8-9).

Glick (Gen. Engineer. News 28(7) pp. 6 and 9 (4/1/08)) recently overviewed the state of art for gene therapy and states: "It was not until the 1960's that the first reports appeared indicating that mammalian cells could be genetically altered by means of isolated DNA. Years later, in 1990, the first successful example of gene therapy was demonstrated, albeit for a very rare, life threatening disorder, severe combined immunodeficiency in a child lacking the normal gene for adenosine deaminase. A fair number of gene therapy clinical trials have been initiated since then and many are ongoing. If perfected, *gene therapy might be of enormous practical value*, saving countless lives and resulting in huge market opportunities. Yet thus far, over 60 years following the discovery that isolated DNA could genetically transform cells, only a handful of companies have marketed gene therapy for a couple of conditions, and the number of patients treated, mostly outside of the U.S., is relatively small."

Thus, at the time the application was filed, the state of the art for gene therapy was considered highly unpredictable.

Unpredictability/ Undue Experimentation

Given the unpredictability of in vivo gene expression (e.g., therapy) starting from in vitro cell-based assays to animal models much less occurring in humans and the insufficient experimental data provided in the specification, the ordinary artisan would be forced into undue experimentation to practice to express the fusion protein in any host cell especially where the expression was to be observed in vivo in any subject.

Conclusion

19. No claims are allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Primary Examiner, Art Unit 1643